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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,712	03/30/2001	Gregor Sagner	5443	7485

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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 12/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/823,712	SAGNER ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-17,23-26 and 31-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17,23-26 and 31-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action filed on October 13, 2005 has been entered.

Status of the Application

2. Claims 15-17, 23-26 and 31-41are pending. Applicants' response to the office action is fully considered and found persuasive in part. All arguments have been fully considered and thoroughly reviewed, but are deemed persuasive in part for the reasons that follow. This action is made FINAL.

3. The following rejections are made in the previous office action:

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15-17, 23-26, 31-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowe et al. (WO 99/54510) in view of Wittwer et al. (USPN. 6,174,670).

Lowe et al. teach a method for determining a quantitative measure of an amplification of a target nucleic acid of claims 15-16, 23-26, 31-33, 38-39 comprising the steps of

(a) preparing a dilution series of the target nucleic acid (see page 3, line 12-14, page 6, line 20-28, page 11, line 24-35);

(b) amplifying the target nucleic acid under defined conditions and measuring the amplification in real-time (see page 3, line 14-25);

(c, d) setting a defined signal threshold value and determining for each dilution, the cycle number at which the signal threshold value is exceeded (threshold cycle for each dilution) (see page 3, line 25-27, page 10, line 16-23);

(f) calculating the amplification equivalent in each dilution series and normalizing the RNA equivalent to provide normalized RNA equivalent standard curve. (see page 3, line 29-33, page 10, lines 31-39).

With regard to claim 23, 25, Lowe et al. teach determining concentration of the target nucleic acid (see page 12, line 9-15);

With regard to claim 31-33, Lowe et al. teach quantifying the amount of target nucleic acid relative to the reference nucleic acid (see page 13, line 30-39, page 14, line 1-19);

With regard to claims 38- 39, Lowe et al teach a method for quantitation of a target nucleic acid using internal standard or reference nucleic acid (see page 13, line 10-39);

With regard to claims 34-35, 40-41, Lowe et al. teach said amplified nucleic acid is detected using fluorescently labeled probe such as TAQMAN probes or FRET probes (see page 10, line 1-30, page 8, line 29-36).

However, Lowe et al. did not teach determining a non-linear continuously differentiable function of a logarithm of copy number and detecting amplified nucleic acid using a DNA-binding dye, SYBR Green I.

Wittwer et al. teach a method of claims 15-17, 23-26, 31-41, for monitoring and quantitating target nucleic acid during real- PCR, wherein Wittwer et al. disclose that the method DNA monitoring at each PCR cycle by measuring melting curves and calculating copy number at each cycle utilizing DNA-binding dye (SYBR Green I), which represents a non-linear continuously differentiable function of logarithm of copy number that is represented as a polynomial fit of copy number of target nucleic acid at each PCR cycle (see col. 3, line 30-61, col. 4, line 45-63, col. 7, line 14-31, Fig. 22-23, Col. 17, line 34-39).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine a method of determining the efficiency of amplification and quantitating a target nucleic acid as taught by Lowe et al. in view of Wittwer et al. with the step of detecting amplified nucleic acid using SYBR Green I dye as taught by Wittwer et al. to achieve expected advantage of developing an improved sensitive method for quantitating a target nucleic acid because Wittwer et al. explicitly taught that the correlation between the threshold cycle and the initial concentration of DNA templates copy number provides precise measurement of abundance of target nucleic acids and its non-linear functionality (3-dimensional spiral) (see col. 4, line 45-63) and SYBR Green I is a preferred double-strand-specific dye for fluorescence monitoring of PCR, primarily because of superior sensitivity, arising from greater discrimination between double stranded and single stranded nucleic acid, and is inexpensive dye (see col. 4, line 45-63, column 23, line 9-16). An ordinary

practitioner would have been motivated to combine the method of determining the efficiency of an amplification of a target nucleic acid and quantitation of said nucleic acid as taught by Lowe et al. in view of Wittwer et al. with the inclusion of determining non-linear continuously differentiable function of logarithm of copy number using SYBR Green I dye as taught by Wittwer et al. for the purpose of enhancing the sensitivity of the method for quantitation of a target nucleic acid and for cost-effective purposes.

Response to arguments:

5. Applicant's arguments filed on 10/13/05 have been fully considered but they are not persuasive. Applicants' argue that the combination of Lowe et al. in view of Wittwer et al. does not teach or suggest the instant claimed invention. Applicants' also argue that the combination does not describe determining a non-linear continuously differentiable function of a logarithm of copy number as a function of the cycle number at which the signal threshold value is exceeded. Applicants further argue that "determining step does not involve copy number at each cycle as the examiner suggests, but instead relies on the initial copy number of each dilution. Applicant's arguments are fully considered and found unpersuasive. First, it is noted that the instant claims (determining step) do not recite determining initial copy number of each dilution, thus the limitation upon which the arguments are based is not *present* in the instant claims. Second, the instant specification does not define "non-linear continuously differentiable function". However it is correlated to a function of the cycle number at which the signal threshold value is exceeded. The specification on page 33, discloses generating a non-linear function with the aid of a polynomial fit of the 4^{th} degree. Further the instant specification discloses determining the signal threshold value as a relative value instead of an absolute value, and the course of the

amplification reaction is determined as a function of the cycle number and hence the method of determining the threshold value is independent of the absolute signal strength of for example fluorescence signal (see paragraph 1 of page 15 of the specification). Thus the strength of fluorescence signal at each cycle as disclosed by Wittwer et al. is considered to determine the threshold value and which is correlated as a non-linear function in terms of polynomial fit as disclosed by Wittwer et al. Thus Wittwer et al. does disclose non-linear function continuously differentiable function of logarithm of copy number. With regard to the arguments directed towards determining initial copy number at each dilution, Examiner notes that the determining copy number at each cycle represents the exponential amplification of initial copy number in each dilution at each cycle.

Applicants further argue that figures 22-23 of Wittwer et al represents cycle number vs fluorescence and not log of initial copy number as recited in the instant claims. Applicant's arguments are found unpersuasive because as discussed above, in the light of the instant specification fluorescence signal strength is considered to determine threshold value and the function of cycle number at which the signal threshold value is exceeded is considered as a non-linear continuously differentiable function of a logarithm of copy number.

Applicants also argue that each plotted line in figures 22-23 of Wittwer is from one amplification reaction and argue that the determining step recited in the claims is based on determining a single function (i.e. single line) representing multiple different amplification reactions having different starting copy number. Applicants also argue that the Figure 23 of Wittwer provides different plots based on initial template copies and does not provide a single plot that provides a function of copy number and cycle number. Applicants' arguments are fully

considered and found unpersuasive. The limitation "single function (single line plot) representing multiple different amplification reactions having different starting copy number" is not present in the instant claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Given the broader scope of the claims the teachings of different plots do not exclude the scope of the instant claims.

Applicants argue that as cited by the examiner, Wittwer does not teach correlation of SyBR Green I in determining non-linear function and argue that the cited paragraph in col.4 of Wittwer et al. discloses monitoring temperature time and fluorescence variables at each cycle, that does not refer to a non-linear equation. Applicants' arguments are fully considered and found unpersuasive because as discussed above fluorescence signal is considered in determining threshold value which is considered in determining non-linear function of a logarithm of the copy number thus monitoring SYBR Green I fluorescence signal at each cycle is considered as a non-linear function. Therefore the Wittwer et al. does teach determining a non-linear function and it is obvious to combine the method of Lowe et al. with the teachings of Wittwer et al. to achieve the instant invention. Thus the rejection is maintained herein.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M , Mon - Friday,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Suryaprabha Chunduru
Patent Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
12/10/04